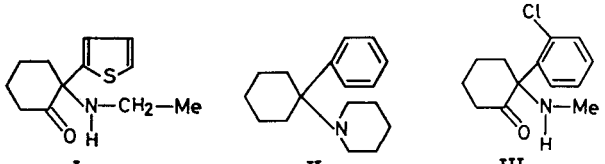
The effects of a phencyclidine derivative, CI-634, on blood pressure in rats

2-(Ethylamino)-2-(2-thienyl) cyclohexanone (CI-634, I) is a derivative of phencyclidine which has been found useful as an intravenous anaesthetic in cats (Chen & Ensor, 1968) and as an immobilizing agent in rabbits (Chen & Bohner, 1968). Phencyclidine (II) is sympathomimetic by an action on the peripheral nervous system, and a rise in blood pressure can be elicited in spinal cats and pithed rats (Ilett, Jarrott & others, 1966). Ketamine (CI-581, III) probably has no peripheral component in its action on the cardiovascular system (Dowdy & Kaga, 1968; Stanley, Hunt & others, 1968). The sympathomimetic effects of CI-634 in rats are now described. To avoid the problems associated with changes in depth of anaesthesia which occur when a drug, known itself to be an anaesthetic, is administered to an anaesthetized animal, CI-634 was injected into acute preparations of unanaesthetized rats. Experiments on urethane-anaesthetized and also in pithed rats were made to assess further the site of action of CI-634.



I CI-634 II Phencyclidine III Ketamine CI-581

Male albino rats (180–200 g) were anaesthetized with ether. The carotid artery was cannulated with a length of nylon tubing and exteriorized. The incision area was filled with gelatin sponge, to reduce bleeding, before closing the opening. The femoral vein was cannulated and the animal wrapped in a black cloth and allowed to recover in a restraining cage. Heparin (1,000 iu/kg) was given intravenously to minimize clotting and blood pressure recorded using a Statham P23AC transducer. Adrenalectomies were made in animals under ether. Rats (250–300 g) were anaesthetized with urethane (0·6 ml/100 g of 20% solution, intraperitoneally) or were pithed by passing a long steel probe through the orbit and down the spinal cord.

In conscious rats, the intravenous injection of CI-634 hydrochloride (1 mg/kg) produced a rise in blood pressure of from 22–35 mm Hg lasting from 10 to 30 min (Fig. 1). There was no tachyphylaxis of this pressor response at 45 min intervals and no potentiation of adrenaline or noradrenaline pressor responses. The pressor response to CI-634 was abolished by pretreatment with 3 mg/kg reserpine given intraperitoneally 24 h previously (Fig. 1). It was not abolished by adrenalectomy. CI-634 (10 mg/kg) produced slight anaesthesia and a depression of blood pressure followed by a slow increase in pressure. CI-634 (20 mg/kg) produced anaesthesia and depression of blood pressure.

In lightly anaesthetized rats, low doses of CI-634 (0·125 and 0·25 mg/kg) caused a biphasic pressor response. If these doses were repeated rapidly, a depressor phase appeared. This triphasic response was also characteristic of the initial response to higher doses (0·5 and 1·0 mg/kg) of CI-634. On repeated dosage with 1 mg/kg the depression of blood pressure became predominant and obscured any pressor response. All the doses of CI-634 examined had no effect on the blood pressure of pithed rats. Responses to CI-634 in anaesthetized rats were abolished by intravenous pentolinium tartrate (3 mg/kg) or hexamethonium bromide (5 mg/kg) or by reserpine-pretreatment.

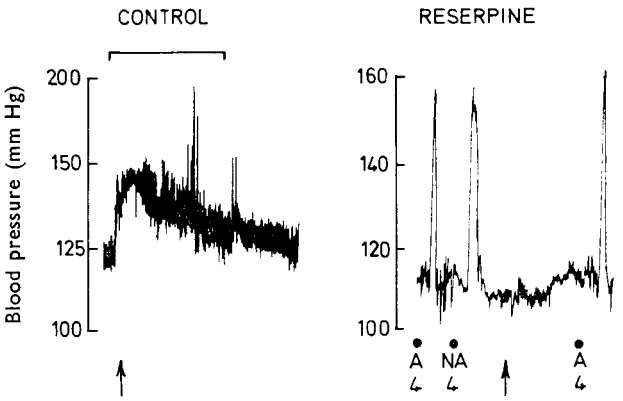


FIG. 1. Blood pressure recordings (mm Hg) from the carotid artery of two conscious rats. CI-634 (1 mg/kg) was administered intravenously at ↑ and 4μg of adrenaline at A and of noradrenaline at NA. The pressor response to CI-634 observed in the control animal was absent in the reserpine-pretreated animal. Time bracket: 10 min.

The rise in blood pressure produced by lower doses of CI-634 is not a peripheral sympathomimetic response since no response to the drug could be elicited in pithed rats. However, the observed block of the pressor response to CI-634 by ganglion blockade and reserpine would suggest involvement of the sympathetic nervous system. Depression of blood pressure produced by anaesthetic doses of CI-634 in conscious rats, and also observed as part of the response in anaesthetized rats, appears to be linked with the anaesthetic properties of the drug. At higher doses of CI-634 or after repeated administration of lower doses, the anaesthetic properties of CI-634 might be expected to summate with urethane to depress blood pressure and also mask pressor responses resulting from other mechanisms. Thus CI-634 requires an intact central nervous system to elicit effects on the blood pressure of rats and in this respect it resembles ketamine more than phencyclidine. Ketamine has been suggested to act either to depress baroreceptor reflex activity (Dowdy & Kaga, 1968) or on central cardiovascular regulatory mechanisms (Stanley, Hunt & others, 1968).

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